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**Section II. (Remarks)**

Claims 1- 42 are pending in the subject application. Claims 1 and 32 have been amended to further recite “and wherein said dermatological composition is free of parabens.” Support for such claim amendment is found in the specification originally filed (at page 2, paragraph [0003], lines 13-15) reciting in relevant part:

[0003] Many such dermatological compositions have been formulated with preservatives such as parabens and other organic chemical compounds. Generally, it is advantageous to formulate dermatological compositions that are free of such preservatives or that otherwise minimize the amounts of such preservatives. [(Emphasis added.)]

In view of the foregoing remarks, no new matter has been introduced by the amendments made to claims 1 and 32.

New claims 40 – 42 are directed to certain aspects of the invention. Claim 40 differs from claim 1 in that glycerin has been deleted from the Markush grouping of humectants recited in claim 1.

Claim 41 is identical to claim 40 except that claim 41 recites the “consisting essentially of” transitional phrase instead of “comprising” recited in claim 40.

Claim 42 is identical to claim 1 except (1) that claim 42 recites the “consisting of” transitional phrase instead of “comprising” recited in claim 1 and (2) that the phrase “and wherein said dermatological composition is free of parabens” has not been recited in view of the use of the transitional phrase “consisting of” in claim 42.

**Claims Rejections under 35 U.S.C. § 102(b)**

Claims 1-3, 5, 7-10 and 35-39 are rejected under 35 U.S.C. § 102(b) as being anticipated by Huard et al. (U.S. Patent no. 6,485,733, hereinafter “Huard”). Applicant respectfully traverses this rejection for the reasons noted below.

In particular, Huard is cited for the proposition that it discloses the composition of Vaseline Intensive Care Extra Strength Lotion which contains glycerin, soybean, urea and sunflower seed oil. For comparison and convenience, the relevant text from Huard is recited below appearing (at column 18, lines 51-63);

Ingredients present in Vaseline® Intensive Care Extra Strength Lotion include (in order of decreasing concentration): water, glycerin, stearic acid, C11-13 isoparaffin, glycol stearate, triethanolamine, petrolatum, sunflower seed oil, glyceryl stearate, soya sterol, lecithin, tocopheryl acetate, retinyl palmitate, urea, collagen amino acids, sodium PCA, zinc oxide,

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cetyl phosphate, magnesium aluminum silicate, fragrance, stearamide AMP, corn oil, methylparaben, DMDM hydantoin, iodopropynyl butylcarbamate and disodium EDTA. Several of these components, in particular, stearic acid, C11-13 isoparaffin, petrolatum, sunflower seed oil contain hydrocarbon chains that contain greater than eight carbon units.” [(Emphasis added.)]

Therefore, Huard is asserted to anticipate claims 1-3, 5, 7-10 and 35-39 under 35 U.S.C §102(b). However, as can be seen from the above-quoted language from Huard, the Vaseline™ Intensive Care Extra Strength Lotion contains methylparaben. Therefore, that composition is not free of parabens.” In response, Applicant has amended independent claims 1 and 32 to recite that the claimed dermatological composition is “free of parabens.” As noted above, such claim amendment is supported by the specification originally filed at page 2, paragraph [0003], lines 13-15.

In view of the foregoing, claim amendments to independent claims 1 and 32 (and to all claims dependent thereon, by virtue of their dependency) Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 1, 3, 5, 7-10 and 35-39 under 35 U.S.C. §102(b) as being anticipated by Huard.

**Claims Rejection Under 35 U.S.C. § 103(a)**

Claims 1-39 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Huard in view of Quan et al. (U.S. Patent No. 6,180,133, hereinafter “Quan”) in view of Durr et al. (U.S. Patent No 5,997,889, hereinafter “Durr”) in view of Hill et al. (U.S. Patent No. 4,233,295, hereinafter “Hill”) and in view of McNulty et al. (US 2005/0048105, hereinafter “McNulty”) for the reasons noted at pages 3-7 of the Office Action. Applicant respectfully traverses this rejection for the reasons noted below.

First, Huard discloses a composition that includes parabens which Applicant’s amended claims expressly exclude. Further, the secondary references (*i.e.*, Quan, Durr, Hill, and McNulty) do not teach exclusion of “parabens” from the Vaseline™ composition noted in Huard. The secondary references are relied upon for incorporating various additional components into the Vaseline™ composition disclosed by Huard. Specifically, the Office Action asserts, in relevant part, the following (at page 4, lines 1-17):

Huard et al. did not specifically teach the incorporation of shea butter, ammonium lactate, butylated hydroxytoluene or sodium polyacrylate into the Vaseline™ composition.

Quan et al. (US 6,180,133 B1) teaches that studies indicated that addition of ammonium lactate to lotions had proven moisturizing activity (col. 3, line 64 – col. 4, line 17).

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Durr et al. (US 5,997,889) disclosed that shea butter may be added to a lotion to improve its moisturizing ability (see Abstract for example).

Hill et al (US 4,233,295) teaches that butylated hydroxytoluene, an antioxidant, is advantageous to incorporate into creams, lotions or ointments in order to preserve the active ingredients therein (see col. 6, lines 23-26).

McNulty et al (US 2005/0048105 A1) teaches that sodium polyacrylate is a known thickening agent for creams and lotions. [(Emphasis added.)]

However, the secondary references do not teach or suggest that “parabens” should be excluded. As such, none of the secondary references in combination with Huard (as applied) – even if combined – arrive at Applicant’s claimed invention which excludes “parabens.” As such, the above-noted references as applied against claims 1-39 do not render these claims obvious under 35 U.S.C. § 103(a).

Applicant’s foregoing comments with regard to the deficiencies of Huard are equally applicable to the instant 35 U.S.C. § 103(a) rejection of claims 1-39 over Huard, in view of Quan, in view of Durr, in view of Hill and in view of McNulty. In particular, the deficiencies of Huard, namely, that the base composition is “free of parabens” is not rectified by any of the secondary references, (*i.e.*, Quan, Durr, Hill or McNulty). Accordingly, Applicant respectfully submits that claims 1-39 are unobvious over the disclosures of the above-noted references in the combination applied.

Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection of claim 1-39 under 35 U.S.C. § 103(a) as being obvious over the applied references.

#### **Additional Comments**

Applicant wishes to direct the Examiner’s attention to the Information Disclosure Statement filed by the Applicant on May 5, 2006. Particular attention is directed to U.S. Patent No. 6,139,850 (hereinafter “Hahn 1”); U.S. Patent No. 5,716,625 (hereinafter “Hahn 2”) and U.S. Patent No. 5,804,203 (hereinafter “Hahn 3”). These three patents purportedly disclose the composition of Vaseline™ Smooth Legs and Feet Lotion. Each of Hahn 1, Hahn 2 and Hahn 3 have similar disclosures with regard to Vaseline™ Smooth Legs and Feet Lotion. Therefore, Applicant will merely refer to the relevant language found in Hahn 1.

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Hahn 1 recites the following relevant language:

f. Post-Shaving Lactic Acid Irritation:

Following a protocol parallel to that of the post-shaving ocean water irritation test described above, a commercial lotion containing 5% lactic acid was applied to contralateral shaved calves of the subject females. The control solution was Vaseline<sup>TM</sup> Smooth Legs and Feet Lotion (containing water, lactic acid (5%), glycerin, isopropyl palmitate, PEG-40 stearate, cetyl alcohol, potassium hydroxide, steareth-2, magnesium aluminum silicate, lecithin, soya sterol, tocopheryl acetate, tetinyl palmitate, dimethicone, menthol, camphor, stearic acid, laureth-7, xanthan gum, polyacrylamide, C13-14 isoparaffin, corn oil, fragrance, DMDM hydantoin, iodopropynyl butylcarbamate, disodium EDTA, PG, and Ext. violet 2); the cation test formulation included strontium nitrate (500 mM) in the same Vaseline lactic acid lotion. 0.5 g of test and control solutions were applied with gloved fingers to the right and left calves. Subjects were asked to rate levels of irritation (sting, burn or itch) on the right calves, and irritation scores were recorded every minute for 10 minutes.” [(col. 22, lines 24 – 45; emphasis Added.)]

In light of Hahn 1, Applicant has introduced new claim 40 wherein the humectant is selected from the group consisting of at least one of urea and ammonium lactate. Note that “glycerin” is not recited in the Markush grouping recited in claim 40. Applicant submits that new claim 40 is patentable over all the references cited in the non-final February 8, 2006 Office Action as well as over Hahn 1, Hahn 2 and/or Hahn 3.

Likewise, new claim 41 reciting “consisting essentially of” language and new claim 42 reciting “consisting of” are patentable over the disclosures of Hahn 1, Hahn 2 or Hahn 3.

With regard to any forthcoming rejection based on a combination of Hahn 1, Hahn 2 and/or Hahn 3 with the above-noted secondary references (*i.e.*, Quan, Durr, Hill and/or McNulty), Applicant submits that there is no independent motivation provided in the references themselves to hand-pick and replace or add only certain components to the Vaseline<sup>TM</sup> Smooth Legs and Feet Lotion described in Hahn 1, Hahn 2, and Hahn 3 without the blueprint provided by Applicant’s claims. Using Applicant’s claims as a blueprint to pick and choose specific components to be replaced or added is tantamount to engaging in the impermissible use of hindsight reconstruction of Applicant’s claimed invention repeatedly prohibited by the Court of Appeals for the Federal Circuit. Sometimes hindsight reconstruction occurs without realizing

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that one has engaged in impermissible reconstruction. Nevertheless, such hindsight reconstruction is not sufficient to set forth a valid *prima facie* obviousness rejection.

For example, Applicant respectfully disagrees that the following assertions in the Office Action provide the requisite independent motivation needed to combine references under 35 U.S.C. § 103(a):

One of ordinary skill in the art would have been motivated to combine ammonium lactate and shea butter into the Vaseline™ [of Huard] composition because they are ingredients well known to improve moisture to the skin.

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the instant ingredients for their known benefit since each is well known in the art for lending moisture protection to the skin. [Office Action at page 4, line 22 to page 5, line 2; emphasis added.]]

What is lost in the above-quoted assertion is that there is no motivation to combine specific ingredients just because the ingredients lend moisture protection. Where is the motivation to use “shea butter” or “ammonium lactate” over potentially hundreds if not thousands of moisturizing ingredients? When the only motivation to hand-pick and add certain specific ingredients is because they are moisturizing – there is no requisite motivation to specifically add ammonium lactate or shea butter.

Similar flaws are found in the other assertions made in the Office Action noted below:

One of ordinary skill in the art would have been motivated to incorporate butylated hydroxytoluene to the Vaseline™ [of Huard] composition in order to preserve the active ingredients therein. [Office Action at page 5, lines 8-10; emphasis added.]]

The Vaseline of Huard already contains a preservative, namely, methylparaben.<sup>1</sup> So, there is no reason or motivation to incorporate another preservative.

Because methylparaben is a recognized “preservative” – **not a thickener** – there is certainly no motivation to replace “methylparaben” with a thickener such as “sodium polyacrylate” as asserted in the Office Action – the relevant language of which is recited below:

One of ordinary skill in the art would have been motivated to add sodium polyacrylate to the Vaseline™ [of Huard] composition, or alternatively, to substitute sodium polyacrylate

<sup>1</sup> Note the attached documents submitted with this paper which corroborate that “methylparaben” is a preservative.

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for another thickener in Vaseline™ [of Huard] such as methylparaben because the addition of the thickening agents to lotions imparts a thicker viscosity to the lotion which has a pleasant consistency and further is easy to administer to the skin and these thickening agents are considered functional equivalents as they perform the same function; thickening the lotion. [Office Action from page 5, line 14 to page 6, line 2; emphasis added.]]

Also, before the Applicant is required to show any “unexpected results”, the Office Action must first establish a proper *prima facie* obviousness rejection. If no *prima facie* rejection is properly established, then the Applicant does not have to rebut the same with any “unexpected results.” What is possibly unknowingly occurring here is the equivalent of putting the “cart before the horse” instead of the other way around which is to (1) first properly establish *prima facie* obviousness (2) before the Applicant is required to rebut the same. Until a proper the *prima facie* rejection is established, Applicant is not required to establish “unexpected results.”

The assertion in the Office Action that:

The choice of thickeners is considered a matter of judicious selection on the part of the ordinary artisan, and no unexpected results can be found by use of sodium polyacrylate, a known cosmetic thickening agent, over thickening agents such as methylparaben which was also a well known thickening agent. [Office Action at page 6, lines 2-5; emphasis added.]]

ignores the concept that picking and choosing specific thickeners must be taught or suggested in the prior art (not in Applicant’s own disclosure) as the motivation to replace or add. Simply stating “matter of judicious choice” is not sufficient to provide the requisite motivation needed to pick and choose specific components to be replaced.

As noted, there is no motivation to replace “methylparaben” – a **non-thickener preservative** – with a **non-preservative thickener** – much less the specific alleged thickener “sodium polyacrylate.” Also, generically speaking, if a thickener is already present, where is the teaching or motivation to even look for a substitute thickener? The foregoing examples illustrate the deficiencies of the obviousness rejections of record. Accordingly, if a further rejection is to be made over Hahn 1, Hahn 2, or Hahn 3, the Office is respectfully requested to appreciate the above-noted deficiencies.

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**CONCLUSION**

In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of all the rejections of record and an indication of the allowance of all the pending claims **1-42** for the reasons noted herein. If any issues remain, incident to the formal allowance of the application, the Examiner is requested to contact the undersigned attorney at (919) 419-9350 to resolve same, so that the patent on this application can be issued at the earliest possible date.

The payment of the fees for adding new claims **40-42** in the amount of (\$ 275) is provided in the attached credit card authorization form. No additional fees are believed to be due. However, should any additional fees be required or an overpayment of fees made, please debit or credit our Deposit Account No. 08-3284, as needed.

Respectfully submitted,



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Date: May 8, 2006

**INTELLECTUAL PROPERTY/  
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Attorney File No.: 4237-101

**Attachments:**

- (1) Credit Card Authorization Form
- (2) Parabens – confirming “methylparaben” is a preservative
- (3) Dorland’s Medical Dictionary – confirming “methylparaben” is a preservative
- (4) Cosmetic and Pharma Preservatives – confirming “methylparaben” is a preservative
- (5) Page 1111 from Remington’s Pharmaceutical Sciences, Mack Publishing Co., Easton, PA (1980) confirming “methylparaben” is a preservative
- (6) Page 1041 from The Merck Index, Merck & Co., Whitehouse Station, NJ (1996) confirming “methylparaben” is a preservative

The USPTO is hereby authorized to charge any deficiency or credit any overpayment of fees properly payable for this document to Deposit Account No. 08-3284

Introduction  
to Hormone  
Disrupting  
Compounds

# Parabens

## Uses

### Home

### Health concerns

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### Take Action! (on FOE Site)

### About this site

This group of chemicals are used as preservatives in cosmetics, and are antibacterial agents in some antibacterial toothpastes. Four main parabens are in use: methyl, ethyl, propyl and butylparabens; many products will have 2 or more of these chemicals as part of a preservative system. As preservatives in cosmetics are on the label in the EU it is easy to find out which products contain these chemicals.

## Oestrogenic effects

In late 1998 John Sumpter's group at Brunel University, UK, published a paper identifying parabens as oestrogen mimics (Routledge et al., 1998). The authors state:

*"Given their use in a wide range of commercially available topical preparations, it is suggested that the safety in use of these chemicals should be reassessed, with particular attention being paid to estimation of the actual levels of systemic exposure of humans exposed to these chemicals. The acquisition of such data is a prerequisite to the derivation of reliable estimates of the possible human risk of exposure to parabens."*

In a screen with a human estrogen receptor expressed by yeast cells the potency of the parabens group was butylparaben>propylparaben>ethylparaben>methylparaben. When methylparaben and butylparaben were injected into immature or ovariectomized rats, butylparaben led to an increase in uterus weights (an oestrogenic effect), whereas methylparaben had no detectable effect.

Another study examining effects on excurrent ducts of the rat testis through puberty to adulthood found no effects from butylparabens (Fisher et al, 1999); however this used much lower doses than the Routledge work.

## Industry response

The European Cosmetic Toiletry and Perfumery Association COLIPA stated that the Routledge work was 'irrelevant' as 'Parabens are hydrolysed in the skin and we have data to show that none are entering the blood stream', and said that the Industry had no plans to follow up the work.

Professor Sumpter replied that

*'What we really want to know is what effects may come from low exposures over*



*a long period of time. That is the realistic exposure mechanism' (ENDS, 1999a).*

AstraZeneca toxicologist Dr John Ashby, who is very engaged in the science and policy debates on endocrine disruption, said at a conference in March that he had decided not to use parabens-containing products on his young daughter (ENDS, 1999b).

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This page was last updated in October 1999

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## References

ENDS, 1999a. Cosmetics and food preservatives are oestrogenic, study finds. ENDS Report 288, p4.

ENDS, 1999b. Industry glimpses new challenges as endocrine science advances. ENDS Report 290, p26-30.

Fisher, J. S., Turner, K. J., Brown, D. and Sharpe, R. M. 1999. Effect of neonatal exposure to estrogenic compounds on development of the excurrent ducts of the rat testis through puberty to adulthood. *Environmental Health Perspectives* 107, p397-405.

Routledge, E. J., Parker, J., Odum, J., Ashby, J. and Sumpter, J. P. 1998. Some alkyl hydroxy benzoate preservative (parabens) are estrogenic. *Toxicology and Applied Pharmacology* 153: 12-19.

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URL: <http://website.llnove.net/~mwarhurst/parabens.html>



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## M

methyclothiazide - mevalonicaciduria

**methyclothiazide** (meth-y-clo-thi-a-zide) (meth'T-klo-thi'e-zid) [USP] a thiazide diuretic used for treatment of hypertension and edema; administered orally.

**methyl** (meth-yl) (meth'al) [Gr. *methy* wine + *hylē* wood] the chemical group or radical —CH<sub>3</sub>, sometimes abbreviated Me.

**m. benzene** toluene.

**m. benzylidene camphor** enzacamene.

**m. bromide** a colorless gas soluble in alcohol and benzene, used in ionization chambers and fire extinguishers and as a reagent and fumigant; it is also found in automobile exhaust. If inhaled in excessive amounts it is neurotoxic, and if a solution touches the skin it causes blistering.

**m. ethyl-pyrrole** a substituted pyrrole obtained from, and probably a constituent of, bilirubin.

**m. hydride** methane.

**m. hydroxy-furfural** the furfural produced from the hexose in Molisch's test and which produces the color.

**m. iodide** a colorless liquid that turns brown on exposure to light, used in microscopy and in testing for pyridine. It is irritating to skin and mucous membranes and is a suspected carcinogen. Called also iodomethane.

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**methylmalonyl-CoA epimerase (meth-yl-mal-o-nyl-CoA epim-er-ase)**

(meth"el-mal'e-nel ko-a' e-pim'er-ās) [EC 5.1.99.1] an enzyme of the isomerase class that catalyzes the equilibration of the D- and L- isomers of methylmalonyl CoA. The reaction is part of the route by which three-carbon compounds from some amino acids and from odd number chain length fatty acids are used as fuels. Called also methylmalonyl-CoA racemase.

**methylmalonyl-CoA mutase (meth-yl-mal-o-nyl-CoA mu-tase) (meth"el-mal'e-nel ko-a' mu'tās)**

[EC 5.4.99.2] an enzyme of the isomerase class that catalyzes the isomerization of L- methylmalonyl coenzyme A to succinyl coenzyme A, requiring adenosylcobalamin as a coenzyme. The reaction is a step in the use of isoleucine, threonine, valine, propionate, and other odd number chain length fatty acids as fuels. Deficiency of enzyme activity, which may be caused by defects in the apoenzyme, in the coenzyme, or in cobalamin metabolism, results in methylmalonicacidemia.

**methylmalonyl-CoA racemase (meth-yl-mal-o-nyl-CoA ra-ce-mase)**

(meth"el-mal'e-nel ko-a' ra'se-mās) methylmalonyl-CoA epimerase.

**methylmercaptan (meth-yl-mer-cap-tan) (meth"el-mēr-kap'tan)**

a gas formed in the intestines by the decomposition of proteins; said to impart to the urine the odor noticed after eating asparagus, and to the breath the characteristic odor of fetor hepatis.

**methylmethacrylate (meth-yl-meth-ac-ry-late) (meth"el-meth-ak're-lāt)**

see under methyl.

**methylmorphine (meth-yl-mor-phine) (meth"el-mor'fēn) codeine.****3-methyl-2-oxobutanoate dehydrogenase (lipoamide) (3-meth-yl-2-oxo-bu-ta-no-ate de-hy-dro-gen-ase (lip-o-am-ide)) (meth"el ok"so-bu'te-no'āt de-hi'dro-jen-ās lip'o-am'īd)**

[EC 1.2.4.4] an enzyme of the oxidoreductase class that is a component of the multienzyme branched-chain α-keto acid dehydrogenase complex (q.v.). The enzyme catalyzes the oxidative decarboxylation of the branched chain amino acids leucine, isoleucine, and valine, transferring the products formed to the lipoic acid moiety of dihydrolipoamide acyltransferase via a thiamine pyrophosphate cofactor. See also maple syrup urine disease, under disease. Called also α-ketoisovalerate dehydrogenase.

**methylparaben (meth-yl-par-a-ben) (meth"el-par'e-ben) [NF]**

an antifungal compound, closely related to butylparaben, ethylparaben, and propylparaben; used as a preservative in pharmaceutical preparations.

**m. sodium** [NF] the sodium salt of methylparaben, having the same actions and uses as the base.

**methylpentose (meth-yl-pen-tose) (meth"el-pen'tōs)**

a hexose derivative in which carbon 6 exists in reduced form, as a methyl group; e.g., fructose. See also deoxyhexose.

**methylphenidate hydrochloride (meth-yl-phen-i-date hy-dro-chlo-ride)**

(meth"el-fen'ī-dāt) [USP] a central stimulant used in the treatment of attention-deficit/hyperactivity disorder, narcolepsy, and certain forms of depression associated with medical conditions which would preclude treatment with conventional antidepressants; administered orally.

**methylprednisolone (meth-yl-pred-nis-o-lone) (meth"el-pred-nis'e-lōn)**

[USP] a synthetic glucocorticoid derived from progesterone, used in replacement therapy for adrenocortical insufficiency and as an antiinflammatory and immunosuppressant in a wide variety of disorders; administered orally.



## PRESERVATIVE A15

Chemical name (C.T.F.A. USA)	Imidazolidinyl urea
Chemical name (U.S.P. NF XVIII)	Imidurea
C.A.S. number	39236-46-9
EINECS Number	2543726
EINECS name	N,N <sup>2</sup> -Methylenbis[ N'-[3-(hydroxymethyl)-2,5-dioxo-4-Imidazolidinyl]urea]
Chemical formula	C <sub>11</sub> H <sub>16</sub> N <sub>8</sub> O <sub>8</sub>
Molecular Weight	388,3

### Properties and uses

Preservative antimicrobial for cosmetics and toiletries. Highly active against a broad spectrum of bacteria gram+ and gram-, yeast and mold. Compatible with most typical cosmetic formulations, active over a wide range of pH and stable in the time, not inactivated by non-ionic emulsifiers and proteins. Highly water soluble, does not migrate into oily phase. For optimum performance suggested use in combination with parabens. May be added at any stage of formulation process as a powder or as a water concentrate at temperature up to 60°C. Recommended 0.1-0.5% by weight on total formulation, alone or best in combination with 0.1-0.2% parabens.

### Toxicological properties

Not irritating to eyes, to human skin at concentrations of use, not sensitizing and not mutagenic by Ames test. Acute oral and dermal toxicity more than 3.000 mgr/kg.

Caution: powder is eyes irritant, in case of contact flush by water, avoid dust inhalation.

The product is hygroscopic, keep tightly closed.

## PRESERVATIVE A2

Chemical name (C.T.F.A.)	Diazolidinyl urea
EINECS Name	Urea,N-[1,3-bis(hydroxymethyl)-2,5- dioxo-4-imidazolidinyl]-N,N'-bis (hydroxymethyl)-
C.A.S. Number	78491-02-8
EINECS Number	2789282
Molecular formula	C <sub>8</sub> H <sub>14</sub> N <sub>4</sub> O <sub>7</sub>
Molecular weight	278.22

### Properties and uses

Preservative A2 is a white hygroscopic powder very water soluble. It is compatible with virtually all cosmetic ingredients. It provides a wide spectrum of antibacterial activity against Gram positive and Gram negative organisms, including *Pseudomonas* species and troublesome "house" organisms and other mutated types. A2 also provides some protection against yeasts and mould. A2 is synergistic with other preservative materials, especially methylparaben and propylparaben. This combination is a complete cosmetic preservative system ( see KEMABEN ) that is effective at protecting well-formulated products from bacterial, yeast and mould contamination during product use. Recommended concentrations 0.1-0.5% by weight on end product, alone or best in combinations with 0.2% parabens.

Granular form available: to reduce dusts in handling and lumping from moisture absorption.

## Kemaben II e Kemaben II E

These products are a combination of the three preservatives most commonly used in the cosmetic industry : Methylparaben, Propylparaben, and Diazolidinyl-urea ( Preservative A2 ).

The liquid system can be incorporated into cosmetic products at any stage of the formulation process.

Suggested level of use: 1% on the finished cosmetic formulation.

In emulsion, it is most convenient added after the heating phase , or during the cooling phase. Its use eliminates the problems associated with incorporating solid parabens into formulations. It minimizes plant error, simplifies inventory control, and effects economies in labor, time and energy consumption.

Its liquid form permits cold formulation of shampoos, liquid soap and other cosmetic products.

The system is useful in preserving cosmetics containing proteins, soluble collagens, aloe, plant and herb extracts, and is effective over a wide pH range.

It is also a valuable preservative for raw material ingredients such as aqueous solutions of anionic and amphoteric surfactants and hydrolyzed animal proteins



16<sup>TH</sup>  
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herein, the context and effect of the official compendia shall prevail.*

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## ANTIMICROBIAL DRUGS 1111

of methenamine to formaldehyde. Hippuric acid is secreted by the renal tubular anion transport system, so that urine concentrations are initially higher than those of mandelic acid from methenamine mandelate. Wide fluctuations in urine levels of hippuric acid are detrimental to the therapeutic action of the methenamine unless the pH of urine stays below 6. Nausea, dysuria, and rash occasionally occur. **Dose:** 1 g 2 times a day. The dose for children of ages 6 to 12 is 500 mg to 1 g 2 times a day.

**Methenamine Sulfosalicylate** [20480-93-7]  $C_8H_{12}N_4 \cdot C_7H_5O_6S$  (358.37); Hexalet (Webcor).—Crystalline powder; 1 g dissolves in 8 ml water; slightly soluble in alcohol. **Uses:** See *Methenamine* and *Methenamine Mandelate* in this section. The sulfosalicylic acid keeps the urine pH low, which not only favors release of formaldehyde but is bacteriostatic as well. **Dose:** Oral, adults, 1 g 4 times a day; children 6 to 12 years of age, 500 mg 4 times a day.

**Methylparaben** [Methyl *p*-hydroxybenzoate [99-76-3]  $C_8H_8O_3$  (152.15); Methyl Parasept; Nipagin M; Solbro].—Prepared by esterification of *p*-hydroxybenzoic acid with methanol. Colorless crystals or white, crystalline powder; faint, characteristic odor; melts at about 126°. One g dissolves in 400 ml water, 3 ml alcohol, 10 ml ether, soluble in glycerin, oils, fats. **Uses:** An antiseptic and preservative used in various pharmaceutical preparations in concentrations of 0.05 to 0.25%; also used in cosmetic preparations containing vegetable and animal fats and oils that are susceptible to decomposition. Where a strong antiseptic effect is desired, 3 to 5 times the usual concentration may be used. Combinations of two or more esters of *p*-hydroxybenzoic acid have a "synergistic" antiseptic action; thus a preparation containing 0.15% of the propyl ester (propylparaben) and 0.05% of the benzyl ester is said to have a stronger antiseptic action than 0.2% of either ester alone. All parabens are capable of sensitizing the skin and inducing cutaneous allergic responses, although the incidence of such reactions is low. Allergy from oral ingestion or parenteral administration has not been reported. Topical antibiotic or corticosteroid preparations may contain 0.3% of parabens. A combination of 0.18% methylparaben and 0.02% propylparaben is approved for use as a preservative for certain parenteral solutions. Methylparaben is used in combination with butylparaben and ethylparaben in some medicaments for pharyngitis. **Dose:** Topical, to pharynx, 3 mg in a troche.

**Oxychlorosene** [8031-14-9]  $C_{20}H_{35}ClO_4S$  (407.02); Clorapactin XCB (Guardian).—Described as a buffered hypochlorous acid derivative of a mixture of long-chain alkylbenzenesulfonates; an antiseptic and surfactant. **Uses:** A topical antiseptic by virtue of its hypochlorite component. Effective against most bacteria and their spores, viruses, yeasts, and fungi. A 0.5% solution in sodium chloride injection is used as a local irrigant during surgery of neoplasms. Solutions of oxychlorosene sodium are used typically for treating localized infections.

**Oxyquinoline** [8-Hydroxyquinoline [148-24-3]  $C_8H_7NO$  (145.14)].—White crystals or crystalline powder; melts at about 76°. Almost insoluble in water, ether; freely soluble in alcohol, chloroform. **Uses:** A bacteriostatic and fungistatic compound; used principally in the treatment of minor burns and of hemorrhoids. **Oxyquinoline sulfate**, which is freely soluble in water and in about 100 parts of glycerin, is variously used, as in the treatment of athlete's foot, vaginitis, and as a gargle, eyewash, nasal douche, and in hemorrhoidal preparations, in the following concentrations: 0.1% in a nasal spray or nasal douche, 0.05% as a gargle, 0.1% as a vaginal douche, 0.033% as an eyewash, 0.15% as a foot powder, and 15 mg in a rectal suppository.

**Parachlorometaxylenol** [4-Chloro-3,5-xyleneol [88-04-0], Chloroxylenol;  $C_8H_7ClO$  (156.61)].—Prepared by treating 3,5-dimethylphenol with chlorine. White crystals or crystalline powder that discolors readily; melts at about 115°. One g dissolves in 3000 ml water, 1 ml alcohol; soluble in ether, fixed oils. **Uses:** A disinfectant active against streptococci but less active against staphylococci and almost inactive against certain gram-negative organisms; inactive against spores; activity reduced in contact with blood or serum. Used for topical antiseptics in the treatment of minor burns, acne, eczema, psoriasis, seborrhea, diaper rash, and in the treatment of athlete's foot. **Dose:** Topical, as 0.3 to 0.5% ointment, cream, lotion; 0.25% powder; 2% shampoo.

**Parachlorophenol** [*p*-Chlorophenol [106-48-9]  $C_6H_5ClO$  (128.56)].—Prepared by chlorination of melted phenol with sulfuric chloride. White or pink crystals with a characteristic phenolic odor; melts at about 42°. Very soluble in alcohol, glycerin, chloroform, ether, fixed and volatile oils; sparingly soluble in water. **Uses:** A local antibacterial agent similar in properties and uses to phenol; the introduction of chlorine in the molecule of phenol increases germicidal activity but the toxicity and caustic action are also increased. It is used principally in dental practice for root canal therapy, in 1 to 5% concentration in various solutions or as camphorated parachlorophenol, which is prepared by triturating 35% of parachlorophenol with 65% camphor until they liquefy.

***p*-Pentoxyphephenol** [18979-53-8]  $C_{11}H_{10}O_2$  (180.24)].—Crystals, melting at about 50°. **Uses:** This antiseptic has a phenol coefficient of 30 against *Staph. aureus* and 29 against *B. typhosus*, demonstrating broad-spectrum antiseptic activity against vegetative organisms. It is not marketed as a single-entity product but is included in powder formulations.

***p*-tert-Pentylphenol** [80-16-6]  $C_{11}H_{14}O$  (164.24)].—A crystalline powder, melting at about 96°. Practically insoluble in water; soluble in alcohol, ether, chloroform. **Uses:** This phenol has broad-spectrum antibacterial activity against vegetative organisms. It is marketed in a lu-

bricant jelly for lubricating endoscopes and for application to the skin and mucous membranes; the jelly contains 0.02% of the phenol and also other antiseptic drugs.

**Poloxamer-Iodine**.—A compound of a type of poly(oxypropylene)-poly(oxyethylene) copolymer (a poloxamer) with iodine; contains approximately 10% of available iodine. **Uses:** An iodophor very similar to Povidone-Iodine in its antiseptic properties and uses. When the two compounds are compared in equal concentrations, poloxamer-iodine yields about twice as high a free-iodine concentration, but the clinical efficacies appear to be the same. **Dose:** Topical, to the skin, the equivalent of 0.76 to 1% iodine (7.5 to 10% of the complex). **Dosage Forms:** Concentrated Liquid: 5%; Surgical Scrub Liquid: 0.76%; Solution: 1%; Swabs: 1%; Whirlpool Additive: 1%. The concentrations indicated are of titratable iodine; for equivalent concentrations of the complex, multiply by 10.

**Potassium Permanganate** [Permanganic acid (HMnO<sub>4</sub>), potassium salt [7722-64-7]  $KMnO_4$  (158.03)].—May be prepared by oxidizing manganese dioxide with potassium chlorate in potassium hydroxide solution, then completing the oxidation with chlorine or air and carbon dioxide. Dark purple crystals or small crystals of dark bronze-like color; 1 g dissolves in 15 ml water. A powerful oxidizing agent that may produce an explosion when triturated with organic matter or other readily oxidizable substances.

**Uses:** A strong oxidizing agent, exerting antibacterial and antifungal actions against organisms susceptible to nascent oxygen. When 0.01% solutions are used the action is slow and may require an hour to be effective; solutions of 0.02% concentration are irritating to tissues. Thus the agent has a low therapeutic index and is best forgotten. It is occasionally used in the treatment of urethritis. Irrigation of the bladder with a solution is sometimes effective in the treatment of persistent urinary infections. It is sometimes employed for the vesicular lesions of epidermophytosis, in the vesicular stage of eczema dermatitis, and in the treatment of ivy poisoning; manganous and manganic ions resulting from reduction of permanganate exert astringent actions in these uses. Potassium permanganate is capable of oxidizing certain drugs and venoms. In the treatment of poisoning following oral ingestion of barbiturates, chloral hydrate, and many alkaloids, gastric lavage with a solution of potassium permanganate helps to destroy the poison and thus prevent absorption. Permanganate solution should not be left in the stomach. Application of permanganate crystals to snake bites to promote oxidation of the venom probably does not destroy the venom sufficiently to affect its actions.

**Dose:** Topical, 0.004 to 1% solution 2 or 3 times a day or in a wet dressing. For urethritis, 0.025%; for bladder irrigation, 0.02%; for ivy poisoning or eczema, 0.01%; for epidermophytosis, 1%; for gastric lavage, 0.02%. **Dosage Form:** Tablets for Solution: 300 mg.

**Propylene Oxide** [Methyloxirane [75-56-9]  $C_3H_6O$  (58.08)].—Prepared by action of aqueous potassium hydroxide solution on propylene chlorohydrin. A colorless, ethereal liquid, extremely flammable; boils at about 34°. Miscible with water (to the extent of about 40% by weight), with alcohol and with ether. **Uses:** Propylene oxide is microbicidal to all microorganisms, including viruses and spores. Because it is a liquid, it is easier to handle than ethylene oxide, but because its boiling point is quite low it can also be used in the vapor phase like ethylene oxide. Its high solubility in water permits its use in solutions. It has the same toxic potential as ethylene oxide, and careful rinsing and/or desorption after its use are necessary. **Application:** As 5% solution with 70% isopropanol or other antiseptics with which it does not react.

**Propylparaben** [Propyl *p*-hydroxybenzoate [94-13-3]  $C_{10}H_{12}O_3$  (180.20)].—Prepared by esterification of *p*-hydroxybenzoic acid with propanol. Colorless crystals or white powder; melts at about 96°. One g dissolves in 2500 ml water, 1.5 ml alcohol, 3 ml ether. **Uses:** An antifungal preservative, often used with Methylparaben.

**Silver Protein, Mild** [9008-39-3] Mild Silver Protein; Mild Protargin; Argyrol (Smith, Miller & Patch)].—Prepared by interaction of silver oxide with a protein in the presence of alkali; contains 19–23% silver, largely nonionized. Dark brown or almost black, shining scales or granules; odorless, frequently hygroscopic, and affected by light. Freely soluble in water, forming a dark-colored solution; practically insoluble in alcohol, chloroform, ether. **Uses:** Formerly widely used in the treatment of conjunctivitis, cystitis, nose and throat infections, and in prophylaxis of gonorrhea. It is now considered archaic. Both local and generalized argyria can follow indiscriminate or long-continued application to mucous membranes. **Dose:** Topical, in 5 to 25% solution to the skin or mucous membranes up to several times a day as required.

**Sodium Benzoate** [532-32-1]  $C_7H_5NaO_2$  (144.11)].—White, granular or crystalline powder; 1 g dissolves in 2 ml water, 75 ml alcohol. **Uses:** Extensively as a food and pharmaceutical preservative, the only one permitted to be used for many classes of food products. To be effective the pH of the preparation in which it is used must not be above 4. It is not bactericidal, only bacteriostatic. It also has fungistatic activity. Sodium benzoate is sometimes used as a test for liver function by measuring the amount of hippuric acid, its metabolite, excreted in urine.

**Sodium Hypochlorite Solution**.—An aqueous solution containing 4.0 to 6.0% w/w of sodium hypochlorite [7681-52-9]  $NaClO$  (74.44). Prepared by electrolysis of a solution of sodium chloride in a cell permitting reaction of chlorine with sodium hydroxide; an equivalent quantity of sodium chloride is simultaneously produced. A clear, pale greenish yellow liquid having a slight odor of chlorine; affected by light. **Uses:** A powerful disinfectant and deodorant, also a bleaching agent. Not only is it ef-

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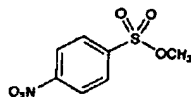
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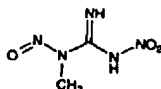
## Methyl Parathion

6183



white to cream crystals, mp 93-95°.  
USE: Methylation agent.

6177. *N*-Methyl-*N*-nitro-*N*-nitrosoguanidine, *N*-Methyl-*N*-nitroso-*N*-nitrosoguanidine; MNNG.  $C_4H_5N_5O_3$ ; mol wt 147.09. C 16.33%, H 3.43%, N 47.61%, O 32.63%. Prepn: A. F. McKay, G. F. Wright, *J. Am. Chem. Soc.* 69, 3028 (1947). Reviews of carcinogenicity and mutagenicity studies: *IARC Monographs* 4, 183-195 (1974); U. Sinha, B. B. Chattop, *J. Sci. Ind. Res.* 3, 499-505 (1975).



Yellow crystals from methanol, mp 118° (dec). Reacts with aq KOH to form diazomethane: A. F. McKay, *J. Am. Chem. Soc.* 70, 1974 (1948). Reacts at acid pH to give methylnitrosoguanidine.

Note: This substance may reasonably be anticipated to be a carcinogen: *Seventh Annual Report on Carcinogens* (PB95-109781, 1994) p 255.

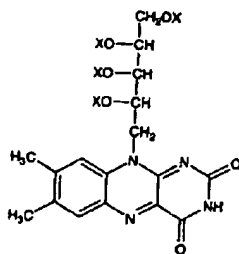
USE: Expetly as carcinogen and mutagen. Formerly in prepn of diazomethane.

6178. Methyl Nonyl Ketone. 2-Undecanone; 2-ben-decanone.  $C_{11}H_{22}O$ ; mol wt 170.30. C 77.58%, H 13.02%, O 9.40%.  $CH_3(CH_2)_9COCH_3$ . Primary constituent of rue oils distilled mainly from *Ruta montana* L. and *R. graveolens*. Prepn: E. v. Gorup-Besanez, F. Grimm, *Ann.* 187, 275 (1871); V. Flaudanese *et al.*, *Tetrahedron Letters* 25, 4805 (1984); T. Aoyama, T. Shioiri, *Synthesis* 1988, 228. LC determ in formulations: R. J. Bushway, *J. Assoc. Offic. Anal. Chem.* 73, 743 (1990). Physical properties: E. Guenther, D. Althausen, *The Essential Oils* vol. 2 (D. Van Nostrand, New York, 1949) p 377. Brief review: D. L. J. Opdyke, *Food Cosmet. Toxicol.* 13, 869-870 (1975).

Oily liquid. Strong odor. mp 12.1°. bp<sub>760</sub> 231.5-232.5°, bp<sub>99</sub> 99°.  $d_4^{20}$  0.8260-0.8263.  $n_D^{20}$  1.42527. LD<sub>50</sub> dermally in rabbits: > 5 g/kg; LD<sub>50</sub> orally in rats, mice: > 5, 3.88 g/kg (Opdyke).

USE: In the compounding of some synthetic essential oils. As fragrance additive in soaps, detergents, creams, lotions, and perfumes. As dog and cat repellent.

6179. Methylol Riboflavin. Hyflavin. Mixture of methylol ( $CH_2OH$ ) derivatives of riboflavin formed by the action of formaldehyde on riboflavin in weakly alkaline soln. The number of methylol groups in the ribityl moiety varies from 1 to 3. Prepn: Schoen, Gordon, *Arch. Biochem.* 22, 149 (1949); U.S. pat. 2,587,533 (1952 to Endo Prod.).

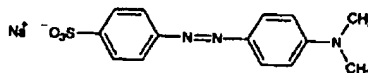


X = H or  $CH_2OH$

Orange to yellow, hygroscopic powder. May have a slight odor of formaldehyde. Sol in water. Practically insol in alcohol, benzene, chloroform, ether. Dextrorotatory. The pH of a 10% aq soln is between 6.7 and 7.9. The dry powder is unstable and loses its biological activity in the course of several months with the liberation of formaldehyde and the partial formation of products practically insol in water.

THERAP CAT: Vitamin (enzyme co-factor).

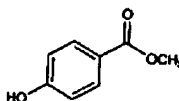
6180. Methyl Orange. 4-[[[4-Dimethylamino]phenyl]-azo]benzenesulfonic acid sodium salt; sodium *p*-dimethylaminoazobenzenesulfonate; helianthine B; C.I. Acid Orange 52; C.I. 13025; Orange III; Gold Orange; Tropaeolin D.  $C_{16}H_{19}N_3NaO_3S$ ; mol wt 327.34. C 51.37%, H 4.31%, N 12.84%, Na 7.02%, O 14.66%, S 9.80%. Prepn from sulfanilic acid sodium nitrite + dimethylaniline: L. Gattermann, *Die Praxis des organischen Chemikers* (de Gruyter, Berlin, 40th ed., 1961) pp 260-261. See also *Colour Index* vol. 4 (3rd ed., 1971) p 4043.



Orange-yellow powder or cryst scales. Sol in 500 parts water; more sol in hot water. Practically insol in alcohol. USE: As indicator in 0.1% aq soln. pH: 3.1 red, 4.4 yellow. Employed for titrating most mineral acids, strong bases, estimating alkalinity of waters; useless for organic acids. In dyeing and printing of textiles.

6181. Methyl Oxalate. Ethanedioic acid dimethyl ester; dimethyl oxalate.  $C_4H_6O_6$ ; mol wt 118.09. C 40.68%, H 5.12%, O 54.19%.  $CH_3OOC-COOCH_3$ . Colorless crystals.  $d_4^{20}$  1.148. mp 54°. bp 163-164°.  $n_D^{20}$  1.379. Sol in 17 parts water, in alcohol, ether.

6182. Methylparaben. 4-Hydroxybenzoic acid methyl ester; methyl *p*-hydroxybenzoate; Nipagin M; Tegosept M; Methyl Chemosept; Methyl Parasept.  $C_9H_{10}O_3$ ; mol wt 152.15. C 63.15%, H 5.30%, O 31.55%. Prepn: Ladenburg, *Fitz. Ann.* 141, 247 (1867); Zbarskii, *C.A.* 33, 9312<sup>3</sup> (1939). Identification in the vaginal secretions of female dogs in estrus: M. Goodwin *et al.*, *Science* 203, 559 (1979).



White needles, mp 131°. bp 270-280° (dec). One gram dissolves in 400 ml water, 40 ml warm oil, about 70 ml warm glycerol; freely sol in alcohol, acetone, ether. The soly in water is also given as 0.25% w/w at 20°, and as 0.30% w/w at 25°.

USE: As preservative in foods, beverages and cosmetics.

6183. Methyl Parathion. Phosphorothioic acid *O,O*-dimethyl *O*-(4-nitrophenyl) ester; *O,O*-dimethyl *O*-*p*-nitrophenyl phosphorothioate; *O,O*-dimethyl *O*-*p*-nitrophenyl phosphate; dimethyl parathion; parathion-methyl; metaphos; E-601; ENT-17292; Dalf (obsolete); Folidol-M; Metacide; Nitrox 80; Penncap M.  $C_8H_{11}NO_3PS$ ; mol wt 263.21. C 36.51%, H 3.83%, N 5.32%, O 30.39%, P 11.77%, S 12.18%. Cholinesterase inhibitor. Prepn: Fletcher *et al.*, *J. Am. Chem. Soc.* 72, 2461 (1950). Manuf: Faith, Keyes & Clark's Industrial Chemicals, F. A. Lowenheim, M. K. Moran, Eds. (Wiley-Interscience, New York, 4th ed., 1975) pp 552-555. Toxicity data: T. B. Gaines, *Toxicol. Appl. Pharmacol.* 14, 515 (1969). Review of carcinogenic risk: *IARC Monographs* 30, 131-152 (1983).

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